

CORRECTED VERSION

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
17 July 2003 (17.07.2003)

PCT

(10) International Publication Number  
**WO 2003/057715 A3**

(51) International Patent Classification<sup>7</sup>: **C12P 19/14**,  
G01N 33/53, C08B 37/00, C07K 2/00

(21) International Application Number:  
PCT/US2002/041588

(22) International Filing Date:  
27 December 2002 (27.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/346,405 28 December 2001 (28.12.2001) US

(71) Applicants (*for all designated States except US*): **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, Oakland, CA 94607 (US). **THE BURNHAM INSTITUTE** [US/US]; 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **FREEZE, Hudson** [US/US]; 211 Garfield Road, San Diego, CA 92110 (US). **SRIKRISHNA, Geetha** [IN/US]; 8503 Villa La Jolla, Apt. F, La Jolla, CA 92037 (US). **VARKI, Ajit** [US/US]; 14042 Rue d'Azur, Del Mar, CA 92014 (US). **VARKI, Nissi** [US/US]; 14042 Rue D'Azur, Del Mar, CA 92014 (US).

(74) Agent: **CARROLL, Peter, G. #**; Medlen & Carroll, LLP, 101 Howard Street, Suite 350, San Francisco, CA 94105 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:  
26 February 2004

(48) Date of publication of this corrected version:  
24 June 2004

(15) Information about Correction:  
see PCT Gazette No. 26/2004 of 24 June 2004, Section II

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL LIGAND INVOLVED IN THE TRANSMIGRATION OF LEUKOCYTES .

(57) Abstract: The present invention provides methods and compositions involved in the inflammatory response, as well as various pathological processes. In particular, the present invention provides novel antibodies directed against novel glycans that are enriched on endothelial cell surfaces. In addition, the present invention provides methods and compositions involved in a previously unrecognized pathway of the inflammatory response and various pathological processes. In addition the present invention provides methods and compositions suitable to mediate the inflammatory response in various settings, as well as methods and compositions for the identification of other inflammatory response mediators.

WO 2003/057715 A3

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
17 July 2003 (17.07.2003)

PCT

(10) International Publication Number  
**WO 2003/057715 A3**

- (51) International Patent Classification<sup>7</sup>: C12P 19/14, G01N 33/53, C08B 37/00, C07K 2/00
- (21) International Application Number: PCT/US2002/041588
- (22) International Filing Date: 27 December 2002 (27.12.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/346,405 28 December 2001 (28.12.2001) US
- (71) Applicants (*for all designated States except US*): **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, Oakland, CA 94607 (US). **THE BURNHAM INSTITUTE** [US/US]; 10901 N. Torrey Pines Road, La Jolla, CA 92037 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **FREEZE, Hudson** [US/US]; 211 Garfield Road, San Diego, CA 92110 (US). **SRIKRISHNA, Geetha** [IN/US]; 8503 Villa La Jolla, Apt. F, La Jolla, CA 92037 (US). **VARKI, Ajit** [US/US]; 14042 Rue d'Azur, Del Mar, CA 92014 (US). **VARKI, Nissi** [US/US]; 14042 Rue D'Azur, Del Mar, CA 92014 (US).
- (74) Agent: **CARROLL, Peter, G. #**; Medlen & Carroll, LLP, 110 Howard Street, Suite 350, San Francisco, CA 94105 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— *with international search report*
- (88) Date of publication of the international search report: 26 February 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL LIGAND INVOLVED IN THE TRANSMIGRATION OF LEUKOCYTES .

(57) Abstract: The present invention provides methods and compositions involved in the inflammatory response, as well as various pathological processes. In particular, the present invention provides novel antibodies directed against novel glycans that are enriched on endothelial cell surfaces. In addition, the present invention provides methods and compositions involved in a previously unrecognized pathway of the inflammatory response and various pathological processes. In addition the present invention provides methods and compositions suitable to mediate the inflammatory response in various settings, as well as methods and compositions for the identification of other inflammatory response mediators.

WO 2003/057715 A3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41588

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12P 19/14; G01N 33/53; C08B 37/00; C07K 2/00

US CL : 435/7.7, 99, 101; 536/123, 123.1; 530/395

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.7, 99, 101; 536/123, 123.1; 530/395

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOOMRE, D.K. et al. Advances in the use of biotinylated diaminopyridine (BAP) as a versatile fluorescent tag for oligosaccharides. Glycobiology. 1994, Vol. 4, No. 5, pages 653-663, especially pages 655-656, entire document.	1-8, 29-32 -----
---		9-22
Y		
X	US 5,449,781 A (VARKI et al.) 12 September 1995 (12.09.1995), column 10, line 45 through column 11, line 25; column 7, lines 8-14.	1-8 -----
---		9-22
Y		
X	ROTHENBERG, B.E. et al. Biotinylated diaminopyridine: An approach to tagging oligosaccharides and exploring their biology. Proceedings of the National Academy of Sciences, USA. December 1993, Vol. 90, pages 11939-11943, entire document.	1-8 -----
---		9-22
Y		

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 October 2003 (07.10.2003)

Date of mailing of the international search report

15 OCT 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Francisco C Prats

Telephone No. 703-308-0196

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/41588

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**Continuation of Item 4 of the first sheet:**

The title is too long, PCT Rule 4.3. New Title: "LIGAND INVOLVED IN THE TRANSMIGRATION OF LEUKOCYTES".

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

The inventions listed as Groups I through VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Toomre et al (Glycobiology 4(5): 653-663 (1994)) disclose BAP-oligosaccharide conjugates containing from 1 to 4 sialic acid residues, i.e., from 1 to 4 negative charges, as required in the claims. See caption of Figure 3 on page 655, disclosing the purification of said BAP-oligosaccharide conjugates using anion exchange HPLC. Product-by-process claims 29 and 32 read on these BAP-oligosaccharide conjugates disclosed by Toomre. Toomre does not mention anything about the claimed leukocyte binding assay (group II), nor does Toomre discuss the preparation of antibodies or monoclonal antibodies or hybridomas from the BAP-oligosaccharide conjugates (groups III and IV), nor does Toomre mention generic methods of reducing extravasation or cell adherence (groups V and VI), nor does Toomre discuss the therapeutic methods recited in the claims (groups VII and VIII).

By disclosing the first-claimed product, without disclosing the numerous direct and indirect applications of that product claimed by applicant, Toomre demonstrates that the first-claimed product lacks a single technical feature which defines it over the prior art. Thus, the listed groups clearly lack a single inventive concept required under PCT Rule 13.1.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-22 and 29-32, drawn to a carboxylated glycan (first product), methods of making and methods of using the glycan (antibody binding assay).

Group II, claim(s) 23-28, drawn to a second method of using the carboxylated glycan (leukocyte binding assay).

Group III, claim(s) 33-52, drawn to antibodies (second product).

Group IV, claim(s) 53 and 54, drawn to hybridoma cell lines (third product).

Group V, claim(s) 55-78, drawn to a method of reducing extravasation of leukocytes.

Group VI, claim(s) 79-87, drawn to a method of reducing adherence of leukocytes to endothelial cells.

Group VII, claim(s) 88-106, drawn to a method of treating inflammation.

Group VIII, claim(s) 107-122, drawn to a method of treating cancer.

**Continuation of B. FIELDS SEARCHED Item 3:**

# INTERNATIONAL SEARCH REPORT

PCT/US02/4

USPAT, US-PGPUB, EPO, JPO, DERWENT, CAPLUS, BIOSIS

search terms: BAP, oligosaccharide, biotin, pyridine, glycan, lung, glycosidase, exoglycosidase, sialidase